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(54) **PROCESS FOR PRODUCING 3-DPA-LACTONE.**

(57) A process for producing 3-DPA-lactone, which is difficult to obtain in a large amount from natural sources, from an easily available starting material in a high yield readily and selectively in a fewer steps than the conventional production processes. The process comprises protecting the hydroxyl groups at the 2- and 5-positions of γ-ribonolactone, eliminating the hydroxyl group at 3-position to form a double bond between the 2- and the 3-positions, reducing this double bond, and removing the protective groups from the protected hydroxyl groups.

EP 0 553 358 A1

Method of preparing 3-DPA-lactone

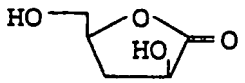
[Technical Field]

The present invention relates to a method of preparing 3-DPA-lactone.

[Background Art]

Recently, in the filed of fine chemicals such as medicines, pesticides and so on, a great attention has been paid on glycoside compounds and sugar-analogue compounds which exist naturally as useful biologically active substances.

A well-known example of the sugar-analogue compounds is (2S, 4S)-2-hydroxy-4-hydroxymethyl-4-butanolide represented by the following formula [5]. The common name of the compound is 3-deoxy pentonic acid lactone, usually abbreviated as 3-DPA-lactone.



[5]

3-DPA-lactone is known as an endogenous feeding promoter substance present in the body fluid of animals. For example, as set forth in the following documents, an increase in the fasting blood concentration of the substance was observed in a rat, and when the substance were administered to a rat, it was observed that feeding behavior of the rat was induced.

(1) Hiroshi OHMURA and Noriaki SHIMIZU; "Chemistry and Biology", Vol. 22, No. 4, page 228

(2) O. Uchikawa, N. Okukado, T. Sakata, K. Arase, K. Terada; "Bull. Chem. Soc. Jpn., 61,2025 (1988)

Therefore, 3-DPA-lactone is an essential substance for making a scientific explanation of feeding behavior of animals including human. The information obtained in the research can be applied widely for development of foods, medicines, and pesticides.

Utilizing its feeding promotion effect, it is possible to promote growth of domestic animals by, for example, mixing the compound into stock feed.

However, 3-DPA-lactone exists in a small amount in nature, and it is difficult to obtain a large amount thereof by extraction from natural material.

Consequently, 3-DPA-lactone must be prepared by a synthetic method. At present, there are two known technigues for preparing 3-DPA-lactone.

One of them is a type in which L-malic acid having an optical activity is used as the starting material [O.Uchikawa, N. Okukado, T. Sakata, K. Arase, K. Terada; Bull. Chem. Soc. Jpn., 61,2025 (1988)]. In this method, a vinyl group is introduced to a carbonyl group of (S)-3,4-O-isopropyliden-3,4-dihydroxybutanal by Grignard reaction so as to form the hydroxyl group corresponding to the hydroxyl group at 2-position of 3-DPA-lactone. Then, the vinyl group is oxidatively cleaved using a Sharpless oxidation into a carboxyl group to form γ-lactone.

The other is a type in which γ-ribonolactone is used as the starting material [K. Bock, I. Lundt, C. Pedersen; Acta. Chem. Scand., B 35, 155 (1981)]. In this method, a hydroxy group of γ-ribonolactone is protected by an acetyl group, and then the γ-ribonolactone is subjected to catalytic hydrogenation at high pressure in the presence of palladium carbon serving as catalyst. Lastly, after removal of the acyl group, 3-DPA-lactone is prepared.

However, each of the above-described methods entails the following drawback.

In the synthetic route of the first method proposed by O. Uchikawa et al., the Grignard reaction is not stereoselective, and therefore two types of diasteromers are formed in respect to the hydroxy group at 2-position. Therefore, it is necessary to separate the two isomers after lactone formation, resulting that the yield of the target product having the S configuration of carbon at 2-position is as low as about 30%. Further, the hydroxyaldehide having an optical activatity, which is the direct raw material, can be obtained through 6 steps from L-malic acid, and the yield thereof is also as low as 25%. In total, it takes 11 steps to prepare 3-DPA-lactone from L-malic acid, and in consideration of having to separate the diastereomers from each other as set forth above, the overall yield will finally be as low as only 4%.

On the other hand, in the synthetic route of the second method proposed by K. Bock et al., hydrogenation must be carried out at a pressure of as high as 100 atmospheres, and therefore, an apparatus used for carrying out the method entails drawbacks in terms of simplicity and safety. In addition,

there are many steps involved in this method, and the yield of the product is low.

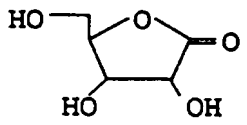
[Disclosure of the Invention]

The object of the present invention is to provide a method of preparing 3-DPA-lactone, in which the target product can be synthesized easily and selectively from a widely available material at a high yield.

The authors of the invention conducted intensive studies to achieve the above object, and have discovered a synthetic route for preparing 3-DPA-lactone by less steps than the conventional preparation method and at a high yield, by using γ-ribonolactone as a starting material, and by performing protection of a hydroxyl group, elimination, catalytic hydrogenation, etc. in a regioselective or stereoselective manner.

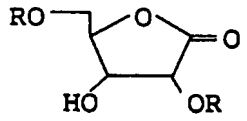
The method of preparing 3-DPA-lactone according to the present invention includes the following steps (a)-(d).

(a) protecting the hydroxyl groups locating at the 2- and 5-positions of γ-ribonolactone represented by the following formula [1],



[1]

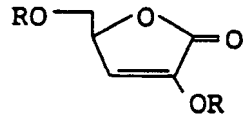
so as to afford a compound represented by the following formula [2],



[2]

(where R represents a protecting group for a hydroxyl group).

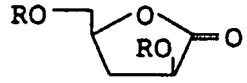
(b) Eliminating the hydroxyl group at 3-position of the compound represented by the above formula [2] so as to form a double bond between the 2- and 3-positions, and thus giving a compound represented by the following formula [3],



[3]

(where R represents a protecting group for a hydroxyl group).

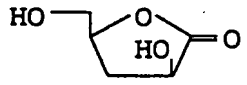
(c) Reducing the double bond between the 2- and 3-position of the compound represented by the above formula [3] so as to give a compound represented by the following formula [4],



[4]

(where R represents a protecting group for a hydroxyl group).

(d) Eliminating the protecting groups of the compound represented by the above formula [4] so as to give a compound represented by the following formula [5],



[5]

The above steps of the method of preparing 3-DPA-lactone according to the present invention will now be described in detail.

In the step (a), a protecting group R is introduced for each of the two hydroxyl groups of γ-ribonolactone represented by the above formula [1].

The protecting group R may be any type as long as it can be used usually for protection of a hydroxyl group, and some of the preferable examples are acetyl, pivaloyl, benzoyl, 3,5-dinitrobenzoyl, and tert-butyldiphenylsilyl.

The solvent used upon introduction of the protecting group R is not particularly limited, but any organic solvents which is generally used can be employed.

The reaction involved in this step may be carried out at a temperature of 0-40 °C, for a time period of 10-120 minutes, using 2-3 equivalents of a reagent containing the protecting group R per one equivalent of the γ-ribonolactone.

In the step (b), the hydroxyl group located at the 3-position of the compound represented by the above formula [2] obtained in the step (a) is eliminated (β-elimination), thereby forming a double bond between 2- and 3-positions.

The β-elimination can be easily performed by converting the hydroxy group at 3-position of the compound of the formula [2] into a leaving group, in the presence of a basic compound.

The leaving group may be arbitrary as far as it is a functional group capable of causing the elimination raction of the hydroxyl group at 3-position in the presence of a basic compound. Some of the examples of the leaving group are acyloxy group, as well as those containing a sulfonyl group which are formed by substituting a hydrogen atom of the hydroxyl group with a mesyl group, tosyl group, trifluoromethanesulfonyl group or the like. Preferable leaving groups are those formed by using a mesyl group, tosyl group, and trifluoromethanesulfonyl group.

The reaction involved in this step should be carried out using 1-10 equivalents of a compound for introducing the leaving group per one equivalent of the compound represented by the above formula [2], at a temperature of 0-40 °C, preferably, room temperature, and for a time period of 0.5-20 hours.

Although not particularly limited to these, liquid tertiary amine compounds such as pyridine, or widely-used organic solvents containing a basic compound can be used as a solvent in the elimination reaction.

Thus, the compound represented by the above formula [3] can be obtained by the β-elimination which is caused by the action of the leaving group in the presence of a basic compound.

It should be noted that the step (b) may not be carried out after the step (a) as a separate step, but may be performed simultaneously with the step (a).

In the following step (c), the double bond between the 2- and 3-positions of the compound represented by the above formula [3] is reduced so as to obtain a compound represented by the above formula [4].

One of the reduction method used here is catalytic hydrogenation, and which can be easily performed by adding the compound together with an appropriate metal catalyst such as platinum, palladium, rhodium, or ruthenium, into an appropriate organic solvent under hydrogen atmosphere, and stirring at about room temperature.

The solvent used here is not particularly restricted, and widely-used organic solvents such as ethyl acetate, ethanol, and methanol can be used.

The reaction in this step should be carried out using 0.01-1 equivalent of the metal catalyst per one equivalent of the compound represented by the above formula [3], at a temperature of 10-40 °C, and for a time period of 0.5-15 hours.

In the final step (d), a protecting group having been introduced to the hydroxyl group at each of the 2- and 5-positions of the compound represented by the above formula [4] is eliminated, thereby obtaining 3-DPA-lactone represented by the above formula [5].

The reaction conditions for eliminating the protection group may those set usually for eliminating an acyl group or silyl group, and are not particularly limited. For example, elimination of an acyl group can be conducted in an aqueous solution under a basic condition using a metal hydroxide such as sodium hydroxide or potassium hydroxide, a metal carbonate such as sodium carbonate or potassium carbonate, a metal alkoxide such as sodium methoxide or potassium butoxide, or ammonium water, or under an acidic condition using a solution containing hydrochloric acid, paratoluenesulfonic acid, or the like, or in an organic solvent such as alcohol under an acidic condition.

The product thus obtained was examined in terms of optical rotation, ^{1}H-NMR spectrum, and ^{13}C-NMR spectrum, and the measured values were compared with the data in the literature [O. Uchikawa, N.Okukado, T.Sakata, K. Arase, K. Terada, Bull.Chem.Soc.Jpn., 61,2025 (1988)]. Thus, it was confirmed that the product was 3-DPA-lactone.

[Best Mode of Carrying Out the Invention]

The present invention will now be described in more detail with reference to an example.

The example discusses a case where the hydroxy group at each of the 2- and 5-positions is protected by a pivaloyl group in the step (a), and an elimination reaction is carried out while converting the hydroxyl group at the 3-position into a mesyl group in the step (b).

〈Step (a)〉

Synthesis of 2,5-O-dipivaloyl-ribonolactone

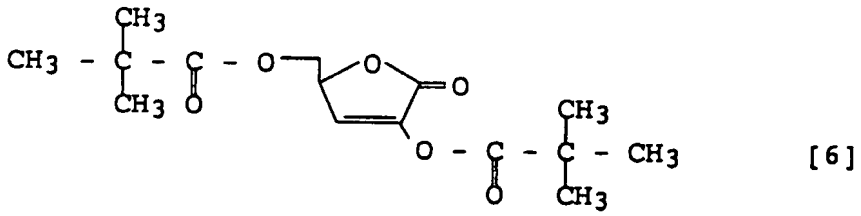
1.03 g (6.75 mmol) of ribonolactone was dissolved into 16ml of pyridine, and 2.04 g (16.89 mmol) of pivaloylchloride was further added dropwise under ice-cooling. The solution was then stirred for 30 minutes at room temperature.

〈Step (b)〉

3.09 g (26.98 mmol) of mesylchloride was added dropwise to the reaction mixture obtained in the step (a) under ice-cooling. The solution was then stirred for 3 hours at room temperature.

The obtained reaction mixture was poured into ice water, and extracted with diethylether. The extract was washed with 1N hydrochloric acid, sodium bicarbonate aqueous solution, water, saturated copper sulfate aqueous solution, and water in the mentioned order, and dried over magnesium sulfate. The solvent was removed by evaporation under a reduced pressure.

Thereafter, the residue was purified by means of silica gel column chromatography (hexane : ethyl acetate = 6 : 1), followed by recrystallization from a hexane:diethylether mixture solvent, thereby giving 1.26 g (the yield from starting material was 62.8 %) of the compound represented by the following formula [6].



[6]

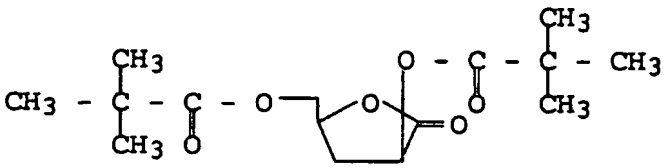
The physico-chemical properties of the compound represented by the above formula [6] are as follows:
Melting Point : 66.0 - 67.5 °C
$[\alpha]_D^{25}$: -32.6° (c = 3.07, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, ppm from TMS):
$(CH_3)_3CO$; 1.18 (9H, s), 1.33 (9H, s),
3-position; 7.14 (1H, d, 3 = 2.0 Hz),
4-position; 5.22 (1H, dd, J = 2.0, 4.1 Hz),
5-position; 4.37 (2H, d, J = 4.1 Hz)

〈Step (c)〉

6.39 g (23.23 mmol) of the compound represented by the above formula [6] was dissolved into 70 ml of ethyl acetate, and 0.70 g of 10% palladium-carbon was further added. The mixture was stirred for 2 hours in a hydrogen gas atmosphere at room temperature.

Thereafter, palladium-carbon was filtrated off from the reaction mixture, and the solvent was removed from the filtrate by evaporation under a reduced pressure.

Thereafter, the residue was purified by means of silica gel column chromatography (hexane : ethyl acetate = 6 : 1), followed by recrystallization from a hexane:diethylether mixture solvent, then 7.16 g of the compound represented by the following formula [7] was obtained.



[7]

The physico-chemical properties of the compound represented by the above formula [6] were as follows:

Melting Point : 78.0 - 80.0 °C

$[\alpha]^{25}D$: +45.9° (c = 3.07, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, ppm from TMS):

$(CH_3)_3CO$; 1.23 (9H, s), 1.26 (9H, s),

2-position; 5.50 (1H, dd, J = 9.0, 10.0 Hz)

3-position; 2.03 (1H, ddd, J = 10.0, 10.0, 12.8 Hz), 2.77 (1H, ddd, J = 6.1, 9.0, 12.8Hz),

4-position; 4.65-4.73 (1H, m),

5-position; 4.20 (1H, dd, J = 5.6, 12.3 Hz), 4.38 (1H, dd, J = 3.3, 12.3 Hz)

〈Step (d)〉

10.55 g of the compound represented by the above formula [7] was dissolved into 53.7 ml of ethyl acetate, and 53.7 ml of 10% sodium hydroxide aqueous solution was further added. The mixture was stirred for 20 hours at room temperature.

Then, the reaction mixture was acidified by adding 1N hydrochloric acid dropwise thereto under cooling the mixture with ice water.

Thereafter, the solvent was removed from the reaction mixture by evaporation under a reduced pressure, and the residue was purified by means of silica gel column chromatography (ethyl acetate). Thus, 4.53 g (yield of 97.6%) of (2S, 4S)-2-hydroxy-4-hydroxymethyl-4-butanolide (3-DPA-lactone) was obtained.

The physico-chemical properties of the obtained compound were as follows:

$[\alpha]^{28}D$: +22.6° (c = 3.07, CH_3OH)

^{1}H-NMR (CD_3OD, ppm from TMS):

2-position; 4.56 (1H, dd, J = 8.6, 10.8 Hz)

3-position; 1.92-2.04 (1H, m),
2.54 (1H, ddd, J = 5.5, 8.5, 12.5 Hz),

4-position; 4.42-4.50 (1H, m),

5-position; 3.59 (1H, dd, J = 5.0, 12.6 Hz), 3.80 (1H, dd, J = 2.8, 12.6 Hz)

^{13}C-NMR [(CD_3OD, ppm from CD_3OD (CD_3 ; 49.8ppm)]: 179.9, 79.4, 70.1, 64.6, 34.4

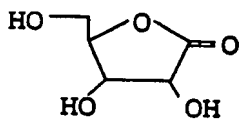
As described above, according to the present invention, there is provided a method of preparing 3-DPA-lactone which is difficult to be obtained in a large amount from nature, in which method the target compound can be synthesized easily and selectively at high yield from a widely available material.

As set forth in the beginning, in the filed of fine chemicals such as medicines, pesticides an so on, a great attention has been paid recently on glycoside compounds and sugar-analogue compounds as useful biologically active substances. In such circumstances, the present invention can easily provide 3-DPA-lactone which is one of the useful bioactive substances, and known as a feeding promoter substance.

Claims

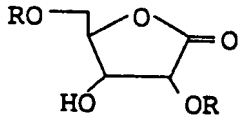
1. A method of preparing 3-DPA-lactone characterized by comprising the following steps (a)-(d):

(a) protecting the hydroxyl groups locating at the 2-and 5-positions of γ-ribonolactone represented by the following formula [1],



[1]

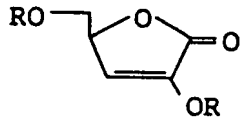
so as to afford a compound represented by the following formula [2],



[2]

(where R represents a protecting group for a hydroxyl group).

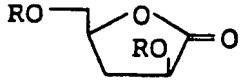
(b) eliminating the hydroxyl group at 3-position of the compound represented by the above formula [2] so as to form a double bond between the 2- and 3-positions, and thus giving a compound represented by the following formula [3],



[3]

(where R represents a protecting group for a hydroxyl group)

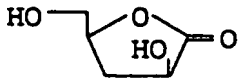
(c) reducing the double bond between the 2- and 3-position of the compound represented by the above formula [3] so as to give a compound represented by the following formula [4],



[4]

(where R represents a protecting group for a hydroxyl group), and

(d) eliminating the protecting groups of the compound represented by the above formula [4] so as to give a compound represented by the following formula [5],



[5]

2. The method of preparing 3-DPA-lactone according to claim 1, characterized in that said protecting group R is selected from the group consisting of acetyl, pivaloyl, benzoyl, 3,5-dinitrobenzoyl, and tert-butyldiphenylsilyl.

3. The method of preparing 3-DPA-lactone according to claim 1, characterized in that in the step (b), elimination of the hydroxyl group at the 3-position of the compound represented by the formula [2] is carried out in the presence of a basic compound by β-elimination after converting the hydroxyl group at the 3-position of the compound represented by the formula [2] into an leaving group.

4. The method of preparing 3-DPA-lactone according to claim 3, characterized in that said leaving group is formed by substituting a hydrogen atom of the hydroxyl group with mesyl group, tosyl group, trifluoromethanesulfonyl group or acyl group.

5. The method of preparing 3-DPA-lactone according to claim 1, characterized in that the step (b) is carried out after the step (a) as a separate step.

6. The method of preparing 3-DPA-lactone according to claim 1, characterized in that the step (b) is carried out in a simultaneous step with the step (a).

7. The method of preparing 3-DPA-lactone according to claim 1, characterized in that reduction of the double bond between the 2- and 3-positions of the compound represented by the formula [3] is performed by catalytic hydrogenation.

8. The method of preparing 3-DPA-lactone according to claim 1, characterized in that in the step (d), the protecting group R for the hydroxyl group of the compound represented by the formula [4] is eliminated by a reaction under a basic condition or acidic condition.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP92/00925

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl[5] C07D307/32

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	C07D307/32

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
P	Heterocycles, 34(2), 363-7(1992)	1-8
A	Bull. Chem. Soc. Jpn., 61(6), 2025-9(1988)	1
A	Acta Chem. Scand., Ser. B, B35(3), 155-62(1981)	1

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
August 3, 1992 (03. 08. 92)	August 18, 1992 (18. 08. 92)
International Searching Authority	**Signature of Authorized Officer**
Japanese Patent Office	